

REMARKS

The Examiner is thanked for the very thorough and professional Office Action and for providing a response to applicants' arguments. The Examiner is also thanked for withdrawing the numerous rejections based in part on the Howey reference and for accepting the substitute drawings filed on April 28, 2008. Claims 1 and 3-20 remain in the application.

Reconsideration is respectfully requested of the rejection of Claims 1 and 12 under 35 U.S.C. 103(a) as being unpatentable over Crawford, et al. in view of Kollias, et al.

Background

The technical level at the time of filing of this application regarding "the percutaneous or transmucosal administration" for a drug using iontophoresis and electroporation is, under the current circumstances, known to be difficult to deliver compounds with a molecular weight of more than 3000 by the combined use of electroporation and iontophoresis. Furthermore, it is also difficult to deliver a sufficient amount of insulin, which has a molecular weight of 6000, through the skin or mucosa as discussed in the several documents mentioned in the specification (see Specification, page 3, lines 20-28). Since the molecular weight of insulin lispro is the same as that of human insulin (molecular weight: 5807), one of ordinary skill in the art would believe that it would be difficult, if not impossible, to deliver a sufficient amount of insulin lispro, even if a combination of electroporation and iontophoresis were used.

The Present Invention

On the other hand, the present inventors attempted to administer various types of insulin, employing iontophoresis and electroporation, singly or in combination (see Specification, page 4, lines 7-14). As a result, it was unexpectedly discovered that when insulin lispro was

administered using electroporation with iontophoresis, excellent percutaneous or submucosis absorptivity of the drug can be achieved. It was also unexpectedly discovered that insulin lispro exhibits sufficient beneficial effects and maintains such effects for a long period when administered in this fashion, thereby completing the present invention (see Specification, page 4, lines 15-24).

The Rejection

In the rejection, the Examiner relies upon the principal reference of Crawford, et al. for the disclosure of using both iontophoresis and electroporosis to administer therapeutic agents. In the office action on page 3, the Examiner concedes that Crawford, et al. “fails to disclose the use of insulin lispro” in the method of administration using iontophoresis and electroporosis.

To cure the deficiencies of the primary reference of Crawford, et al., the Examiner then relies upon the secondary reference of Kollias, et al. for the proposition that “Kollias teaches use of insulin lispro (Paragraph 28 and 70, fast acting insulin also referred to as lispro is used in reference with electroporosis and iontophoresis)”

Argument

It is respectfully submitted that this rejection raises a number of important factual and legal issues as follows:

1. Whether the references considered as a whole provide a correct factual basis for the rejection as set forth in the office action by the Examiner.
2. Whether any prima facie case of obviousness is refuted by objective evidence of non-obviousness, and

3. Whether the rejection fails, as a matter of law, for failing to comply with the factual inquiries set forth in *Graham v. John Deere Co.*, 383 US 1, 148 USPQ 459 (1966).

Applicants respectfully submit that the answer to these issues is in the negative with respect to the first issue, and in the affirmative with respect to the second and third issues, for the reasons discussed hereinafter.

The Crawford, et al. Reference

Crawford, et al. disclose delivering drugs, pharmaceuticals, plasmids, genes and other agents into living bodies using the combination of iontophoresis and electroporation. In this connection Crawford, et al. disclose numerous human maladies for which drugs are delivered, including open heart surgery and chemotherapy (column 3, lines 24-48, and column 5, lines 1-7).

However, there is no disclosure whatever in Crawford, et al. of combining iontophoresis and electroporation in the treatment of diabetes, nor is there any disclosure of administering either human insulin or synthetic analogs of human insulin for the treatment of diabetes.

In view of the known difficulty of administering a high molecular weight compound with a molecular weight of almost 6,000 using either electroporation or iontophoresis, it is respectfully submitted that one of ordinary skill in the art with only Crawford, et al. before them would not consider it obvious to combine iontophoresis and electroporation for the treatment of diabetes with insulin lispro. On the contrary, it is respectfully urged that one of ordinary skill in the art would not use either electroporation or iontophoresis for treating diabetes because of the difficulty in delivering a sufficient amount of high molecular weight insulin lispro by this method of administration.

The Kollias, et al. Reference

In the rejection the Examiner argues that Kollias, et al. “teaches use of insulin lispro (Paragraph 28 and 70, fast acting insulin also referred to as lispro is used in reference with electroporosis and iontophoresis)”. It is respectfully submitted that the Examiner’s reliance upon Kollias, et al. is misplaced because Kollias, et al. neither teach the use of insulin lispro nor that a fast-acting insulin can be used with electrotransport as contended by the Examiner in the paragraph bridging pages 11 and 12 of the office action.

In paragraph 70 of Kollias, et al. it states, “subcutaneous injections of fast-acting insulin (21U, Regular Iletin® II, U-100, Pork, Eli Lilly, Indianapolis, Ind.) were administered to four pigs”. It is respectfully urged that “fast-acting insulin” does not mean insulin lispro. Attached hereto as Exhibit A is a copy of the package of “Regular Iletin® II”, which also has marked on it “Insulin Injection, USP Purified Pork”.

Also attached hereto is Exhibit B which is a copy of the package of “NPH Iletin® II” which also has marked on the package, “Isophane Insulin Suspension, USP Purified Pork”. Please note that the expression “insulin lispro” does not appear on either of these packages in Exhibits A and B.

Also attached hereto is an Exhibit C which contains a title page for the United States Pharmacopeia, 2004 edition, as well as the Notice and Warning page for patent and trademark rights and pages 983-986. It can be seen from Exhibit C that the United States Pharmacopeia distinguishes insulin lispro (see page 985) from insulin injection (see page 983) and isophane insulin suspension (see page 986). On the basis of these exhibits, A-C, it is respectfully urged that one of ordinary skill in the art would not confuse insulin injection with insulin lispro or isophane insulin. It is also respectfully urged that one of ordinary skill in the art would understand that fast-acting insulin

(Regular Iletin® II) in Kollias, et al. is different from insulin lispro. In general terms, insulin lispro is not fast-acting insulin, but rather ultra-fast-acting insulin.

Moreover, the discussion in paragraph 70 of Kollias, et al. does not disclose using insulin lispro with electroporation and iontophoresis, but rather fast-acting insulin (Regular Iletin® II) with “subcutaneous injections”. Further, it is strongly urged that the description in paragraph 70 of Kollias, et al. is independent of that of paragraph 28 in Kollias, et al. For these reasons, it is respectfully urged that the Examiner’s interpretation of Kollias, et al. is erroneous, especially when considered in light of attached exhibits A, B, and C. Accordingly, it is strongly urged that Kollias, et al. do not teach that insulin lispro can be used with electrotransport.

In view of this more complete analysis of Kollias, et al. above, it is respectfully submitted that insulin lispro would not be considered by one of ordinary skill in the art as an equivalent substance for insulin. It is therefore believed that the factual basis for the Examiner’s rejection is erroneous because Kollias, et al. does not describe the use of insulin lispro in electrotransport. It is therefore equally clear that insulin lispro is not equivalent to insulin. For these reasons, it is believed that the Examiner would be justified in no longer maintaining this rejection.

Objective Evidence Of Non-Obviousness

In determining whether the subject matter as a whole is obvious, all evidence bearing on the subject must be considered. *In re Soni*, 54 F3d 746 (CAFC 1995). Proof of an unexpected improvement can rebut a prima facie case of obviousness. *In re Murch*, 175 USPQ 89 (CCPA 1972).

No matter how strong the prima facie case of obviousness made out by the U.S. PTO, it must be weighed by any factors to the contrary brought out by the applicant in determining the validity of the conclusion of patentable unobviousness. *In re Lewis*, 170 USPQ 84 (CCPA 1971).

In the present case, the application sets forth numerous examples and comparative examples in which electroporation-iontophoresis as well as iontophoresis individually and electroporation individually were used in the administration of insulin and lispro. In Example 1 and comparative examples 1 and 2, a solution containing approximately 500 units of insulin lispro was used. In comparative example 3, a human insulin solution was used having a concentration of approximately 500 units/mL. In Example 2 and comparative example 4, a commercially available 100 units/mL Humalog was used.

Further, in comparative examples 5-7, various types of insulin were adjusted to have a concentration of 200 units/mL. An insulin-administering device containing these formulations was used to administer to the abdominal region of SD rats. Blood was collected from the carotid arteries of the rats over time, and the level of insulin lispro in the blood and the level of glucose therein were measured.

In Example 2 an experiment was carried out in the same manner as Example 1, except that the unit of the insulin lispro solution administered was set at 100 units/mL.

In Comparative Example 1, only iontophoresis was used in the administration. In Comparative Example 2, only electroporation was used. In Comparative Example 3, only human insulin was used. In Comparative Example 4, only human insulin was used, and in Comparative Example 5, only swine insulin was used. In Comparative Example 6, bovine insulin was used. In Comparative Example 7, arginine insulin was used. The data obtained from these tests and measurements was then plotted in graphs.

Each of Examples 1, 2, and Comparative examples 3-7, uses the combined electroporation and iontophoresis.

Fig. 9 is a graph showing the level of insulin in the blood in Example 1 (insulin lispro) and Comparative example 3 (human insulin). Fig. 10 is a graph showing a change in the level of glucose in the blood in Example 1 and Comparative example 3, as a ratio of the blood glucose level after administration to the blood glucose level at the initial stage (before administration). According to Figs. 9 and 10, it was found that, although electroporation and iontophoresis are used in combination, sufficient absorption cannot be achieved unless a drug to be administered is insulin lispro.

Fig. 11 is a graph showing the level of insulin in the blood in Example 2 (insulin lispro) and Comparative Example 4 (Humalin). According to Fig. 11, it is found that, even though the concentration of insulin administered in Example 2 was set at one-fifth ($1/5$) of the concentration in Example 1, the maximum blood insulin level was approximately $700 \mu\text{U/mL}$, and thus, when compared with Comparative Example 4, extremely high absorption of insulin was achieved in Example 2.

Fig. 12 is a graph showing a change in the level of glucose in the blood in Example 2 (insulin lispro) and Comparative examples 4 (Humalin), 5 (swine insulin), 6 (bovine insulin), and 7 (arginine-insulin), as a ratio of the blood glucose level after administration to the blood glucose level at the initial stage (before administration). According to Fig. 12, it is found that, only in the case of using insulin lispro, the glucose level was decreased to 20% of the initial value, but when other types of insulin were used, a decrease in the glucose level was only 65% of the initial value.

It is respectfully submitted that this experimental data confirms that unexpectedly high absorption of insulin can be achieved only when insulin lispro is administered by using in combination the electroporation capable of applying a high electric field for a very short time and

iontophoresis capable of applying a low electric field for a longer period. Also, high beneficial effects were confirmed by this data. When either the iontophoresis or the electroporation was used individually, no effects could be obtained. Although both means were used in combination, absorption was insufficient in the case of administering other types of insulin other than insulin lispro.

It is, therefore, respectfully submitted that these tests demonstrate the unexpected results obtained by the combined use of electroporation and iontophoresis to enable significantly high absorption of insulin lispro, when it is administered percutaneously or transmucosally.

In view of these startling and unexpected findings, it is respectfully urged that this objective evidence rebuts any prima facie case of obviousness made out by the Examiner's combination of references. For these reasons, the rejection fails, as a matter of law, in view of the above authorities. Consequently, the Examiner would be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

The Rejection Fails To Comply With *Graham v. John Deere Co.*, 383 US 1 (1966)

In the recently published "Examination Guidelines For Determining Obviousness Under 35 U.S.C. 103 In View Of The Supreme Court Decision in *KSR International Co. v. Teleflex, Inc.*", (Federal Register/Vol. 72, No. 195/October 10, 2007/Notices) the U.S. PTO stated:

"To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:

(1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior

art being the lack of actual combination of the elements in a single prior art reference;

(2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately;

(3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.”

As rationale for the above requirements the office relied upon the authority of KSR at 82 USPQ 2d at 1395 (2007); *Sakraida v. AG Pro, Inc.*, 425 US 273, 189 USPQ 449, 453 (1976); *Anderson's – Black Rock, Inc. v. Pavement Salvage Co.*, 396 US 57, 62-63, 163 USPQ 673, 675 (1969); and *Great Atl. & Pac. Tea Co. v. Supermarket Equip. Corp.* 340 US 147, 152, 87 USPQ 303, 306 (1950).

In the present case, it is respectfully and sincerely urged that the rejection based on Crawford, et al. in view of Kollias, et al. utterly fails to comply with the requirement for a *Graham* factual inquiry as discussed above. Most important is the fact that these prior art references do not include each element claimed as pointed out above. Moreover, the rejection fails to make a finding that each element (insulin lispro) would have performed the same function as (insulin injecton) in the references. Further, the rejection fails to make a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable, i.e., that using iontophoresis and electroporation would affect the administration of a sufficient amount of the drug. Consequently, it is respectfully submitted that the rejection fails, as

a matter of law, in view of the above authorities. Withdrawal of the rejection is respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 3,4, 15-17 and 20 under 35 U.S.C. 103(a) as being unpatentable over Crawford, et al. in view of Kollias, et al. and in further view of Mori, et al.

The deficiencies of each of Crawford, et al. and Kollias, et al. are discussed in detail above.

Recognizing the deficiencies of these references, as discussed above, the Examiner then relies on the additional secondary reference of Mori, et al. to cure these deficiencies. Although Mori, et al. disclose that insulin can be administered with the combination of iontophoresis and electroporation, there is no disclosure whatever in Mori, et al. that the combined use of iontophoresis and electroporation could be used to successfully administer a sufficient amount of insulin lispro to a patient. On the contrary, that particular teaching comes only from the present application and constitutes an important element or aspect of the present invention.

Failing such a disclosure, it is respectfully submitted that Mori, et al. fail to cure the deficiencies of the Examiner's combination of Crawford, et al. and Kollias, et al. Consequently, it is respectfully submitted that the rejection fails for the reasons set forth above. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 5-6 under 35 U.S.C. 103(a) as being unpatentable over Crawford, et al. in view of Kollias, et al., and in further view of Jacobsen, et al.

The deficiencies of the Examiner's combination of Crawford, et al. and Kollias, et al. are discussed above.

The Jacobsen reference, like the other references supplied by the Examiner, also fails to disclose administration of insulin lispro by iontophoresis and electroporation. That teaching comes only from the present application and is in no way found in any of the references applied by the Examiner. Consequently, the Examiner would be justified in no longer maintaining the rejection. Withdrawal of the rejection is therefore respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 7-10 and 18 as being unpatentable over Crawford, et al. in view of Kollias, et al., and in further view of Mori, et al.

The combination of Crawford, et al. and Kollias, et al. is discussed above.

The secondary reference of Mori, et al. fails to cure the deficiencies of the Examiner's combination of Crawford, et al. and Kollias, et al. as discussed above. Consequently, the Examiner would be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claims 11 and 19 as being unpatentable over Kollias, et al. in view of Crawford, et al., in further view of Mori, et al., and in further view of Murdock.

The deficiencies of the Examiner's combination of Crawford, et al., Kollias, et al., and Mori, et al. are discussed above in detail.

Although the Murdock reference does disclose the use of a dry drug in a reservoir in iontophoresis, Murdock fails to cure the deficiencies of the other references as discussed above, i.e., the administration of insulin lispro using a combination of iontophoresis and electroporation. Consequently, the Examiner would be justified in no longer maintaining this rejection. Withdrawal of the rejection is accordingly respectfully requested.

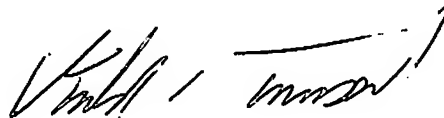
Reconsideration is respectfully requested of the rejection of claims 13 and 14 as being unpatentable over Crawford, et al., in view of Kollias, et al., in further view of Miller, et al., in further view of Murdock.

The deficiencies of Crawford, et al. and Kollias, et al. are discussed above.

The Miller, et al. reference fails to cure the deficiencies of Crawford, et al. and Kollias, et al., i.e., Miller, et al. fail to disclose the administration of insulin lispro using iontophoresis and electroporation. The power supply of Miller, et al. fails to cure many of the basic deficiencies of the Examiner's other references. Consequently, the Examiner would be justified in no longer maintaining the rejection. Withdrawal of the rejection is accordingly respectfully requested.

In view of the foregoing, it is respectfully submitted that the application is now in condition for allowance, and early action and allowance thereof is accordingly respectfully requested. In the event there is any reason why the application cannot be allowed at the present time, it is respectfully requested that the Examiner contact the undersigned at the number listed below to resolve any problems.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Donald E. Townsend', with a stylized flourish at the end.

Donald E. Townsend
Reg. No. 22,069

Customer No. 27955

Date: December 15, 2008

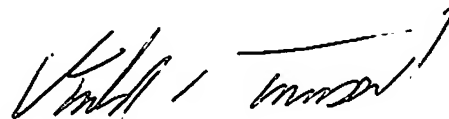
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CERTIFICATE OF MAILING

I hereby certify that this Response and attached Exhibits A, B, and C in Docket No. MUR-043-USA-P, Serial No.10/510,694, filed October 8, 2004, is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to:

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

On December 15, 2008 .

A handwritten signature in black ink, appearing to read 'Donald E. Townsend', is written over a horizontal line.

Donald E. Townsend
Reg. No. 22,069